REMARKS

This paper is being presented in response to the non-final official action dated October 22, 2004, wherein: (**a**) claims 1-17, 32-37, 39-41, 44-51, 54, 56, and 57 are pending; (**b**) the pending claims have been rejected for alleged noncompliance with the statutory written description requirement under 35 USC § 112, ¶ 1; and, (**c**) the pending claims have been rejected under 35 USC § 103(a) as being obvious over Gehlert et al. U.S. Patent No. 5,281,624 or Foreman U.S. Patent No. 5,441,985, each in view of Dostert *et al.* (1997) *Euro. Neuropsychopharmacol* **7**:s23-s35. Reconsideration and withdrawal of the rejections are respectfully requested in view of the foregoing amendments and following remarks.

This paper is timely filed as it is accompanied by a petition under 37 CFR § 1.136(a) for an extension of time to file in the second month, and payment of the required extension fee.

The official action acknowledges the September 8, 2004, supplemental information disclosure statement (IDS) and the documents identified therein, but does not acknowledge the August 26, 2004, supplemental IDS and the documents identified therein. Accordingly, the applicants hereby request consideration of the August 26, 2004, supplemental IDS and the documents identified therein, and request that the U.S. Patent and Trademark Office (PTO) provide the applicants with an examiner-initialed copy of the same with the next action on the merits.

I. Brief Summary of the Amendments to the Claims

Dependent claim 13 has been canceled. Independent claim 1 has been amended to incorporate the subject matter originally recited in now-canceled, dependent claim 13. Dependent claim 12 has been amended to correct a typographical error in the spelling of the term "intravenously," and dependent claims 14 and 15 have been amended to now depend from amended claim 1.

Dependent claims 2-8 have been amended to clarify that it is the optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof, that is administered in the recited amounts. Support for the amendments to these claims can be found in the specification at, for example, page 24, line 12, to page 25, line 3.

Dependent claims 15-17 have been amended to clarify that the percentages recited therein are based upon the total amount of reboxetine present. Support for the amendments to these claims can be found in the specification at, for example, page 16, lines 22 and 23.

Independent claim 39 has been amended to improve its clarity by removing the redundant recitation "said optically pure (S,S) reboxetine being substantially free of (R,R)

reboxetine." Support for the amendment can be found in the specification at, for example, page 16, lines 10-13.

In addition to claim 13, claims 32-37, 41, 44-51, and 57 have been canceled herein without prejudice to filing a continuing application directed to the subject matter of these claims.

Claims 58-71 have been added herein and are either directly or indirectly dependent upon claim 39. Claims 58-71 mirror dependent claims 3-12 and 14-17.

No new matter has been introduced by this paper.

By the foregoing amendments, fourteen dependent claims are being newly-added and seventeen dependent claims are being cancelled. Accordingly, no fee is believed to be due in view of the foregoing amendments.

II. The 35 USC § 112, ¶ 1, Rejection is Moot

All pending claims (claims 1-17, 32-37, 39-41, 44-51, 54, 56, and 57) have been rejected for alleged noncompliance with the statutory written description requirement under 35 USC § 112, ¶ 1. *See* the Action, at pp. 2-3.

The propriety of the bases for the rejection is not conceded. However, in an effort to advance this application toward allowance, and as noted above (Section I), claim 1 has been amended to incorporate the subject matter originally recited in the now-cancelled, dependent claim 13. Accordingly, claim 1 now recites a method of treating an individual suffering from incontinence, wherein the method includes administering to the individual a therapeutically effective amount of a composition containing an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof. As amended, the claim finds adequate written description support under § 112, ¶ 1, at, for example, page 11, lines 11-13, of the specification, which states that "[a]n example of a compound having a pharmacological selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000, is optically pure (S,S) reboxetine." Accordingly, the rejection is now moot, and reconsideration and withdrawal of the rejection are respectfully requested.

III. The 35 USC § 103(a) Rejections Are Traversed

All of the pending claims have been rejected under 35 USC § 103(a) as being obvious over Gehlert et al. U.S. Patent No. 5,281,624 or Foreman U.S. Patent No. 5,441,985, each in view of Dostert *et al.* (1997) *Euro. Neuropsychopharmacol* **7**:s23-s35, (hereafter the "1997 Dostert article"):

> The prior art teaches that tricyclic anti-depressant compounds with norepinephrine reuptake inhibitory activity have been previously used for the treatment of lower urinary tract disorders. The prior art also makes clear that reboxetine is a tricyclic anti-depressant having norepinephrine reuptake inhibitory activity. Although, the prior art raises the question of the possibility of the involvement of other mechanism in treating urinary incontinence, but the inhibition of norepinephrine reuptake in treating urinary incontinence is acknowledged by the prior art. Thus, the substitution of one norepinephrine reuptake inhibitor for another would have been obvious to a person skilled in the art in the absence of evidence to the contrary. Applicant has presented no evidence to establish the unexpected or unobvious nature of the claimed invention, and as such, [the pending claims] are properly rejected under 35 U.S.C. 103.

See the Action, at pp. 3-4.

Briefly, none of the applied publications, either alone or when combined, discloses or suggests that a potent norepinephrine reuptake inhibitor that is highly selective against the serotonin and other monoamine receptor sites will provide advantages (e.g., enhanced efficacy, reduced incidents of side effects) in treating urinary incontinence. Furthermore, none of the applied publications, either alone or when combined, discloses or suggests that (S,S) reboxetine possesses such highly selective properties that are advantageous in treating urinary incontinence. Still further, none of the applied publications, either alone or when combined, discloses or suggests the use of (S,S) reboxetine in treating urinary incontinence. Consequently, the § 103(a) rejections are strongly traversed, especially in view of the claim amendments presented herein.

A complete response to the § 103(a) rejections is set forth below.

A. Proper Basis for a § 103(a) Rejection

The PTO "has the burden under § 103 to establish a prima facie case of obviousness." *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). To establish a prima facie case of obviousness, the PTO must satisfy three basic criteria. First, the PTO must show that the combined disclosure of the prior art references teaches or suggests all of the claim limitations. *See* MPEP § 2143 (8th ed., May 2004). Moreover, it is "incumbent upon the

examiner to identify wherein each and every facet of the claimed invention is disclosed in the applied reference." *Ex parte Levy*, 17 USPQ2d 1461, 1462 (Bd. Pat. App. & Inter. 1990).

Second, where obviousness is alleged to arise from a combination of elements across a plurality of references, the PTO must show the existence of some suggestion, motivation, or teaching to those skilled in the art to make the precise combination recited in the claims. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1320 (Fed. Cir. 2004). Compliance with this requirement prevents the PTO's use of "the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability — the essence of hindsight." *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1371-72 (Fed. Cir. 2000) (quoting *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999)). Evidence of a suggestion or motivation to combine prior art references may come from "the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved." *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000). The PTO's showing "must be clear and particular, and broad conclusory statements about the teaching of multiple references, standing alone, are not 'evidence.'" *Id.* (quoting *In re Dembiczak*, 175 F.3d at 1000). Indeed, the U.S. Court of Appeals for the Federal Circuit has consistently held that a person having ordinary skill in the art must not only have had some motivation to combine the prior art teachings, but also some motivation to combine the prior art teachings **in the particular manner claimed**. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000) ("Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination **in the manner claimed.**" (emphasis added)).

To support a conclusion that a claimed combination is prima facie obvious, either (a) the references must expressly or impliedly suggest the claimed combination to one of ordinary skill in the art, or (b) the PTO must present a convincing line of reasoning as to why a person of ordinary skill in the art would have found the claimed invention to have been obvious in light of the teachings of the references. *See Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985); *see also, In re Rinehart*, 531 F.2d 1048, 1051 (CCPA 1976). The mere fact that the prior art could be modified as proposed by the PTO is not sufficient to establish a prima facie case of obviousness. *See In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992). The PTO must explain why the prior art would have suggested to one of ordinary skill in the art the desirability of the modification. *Id.*; *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998) ("In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination **in the manner claimed**." (emphasis added)).

Finally, the PTO must demonstrate that a person having ordinary skill in the art would have a reasonable expectation of success when combining the disclosures of the references. The suggestion or motivation to make the claimed invention and the reasonable expectation of success must both be found in the prior art, and must not be derived by hindsight from knowledge of the application's disclosure. *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); MPEP § 2143.

B. The Pending Claims Are Not Prima Facie Obvious

Currently, the alleged prima facie case of obviousness is premised on the combination of elements purportedly found in (a) one of the Foreman and Gehlert patents and (b) the 1997 Dostert article; a purported suggestion/motivation therein to make the precise combination recited in the pending claims; and, a reasonable expectation by a hypothetical person having ordinary skill in the art as of the filing date of the application — but not having knowledge of the disclosure found in the application — that the precise combination will yield successful results. For the reasons set forth below, the pending claims are not prima facie obvious. Furthermore, even if a prima facie case of obviousness could be made based on the combined disclosures of the applied publications, evidence of unexpected results effectively rebuts that case warranting a finding that the pending claims are unobvious over the combined disclosures of the applied publications. Accordingly, reconsideration and withdrawal of all of the § 103(a) rejections are respectfully requested.

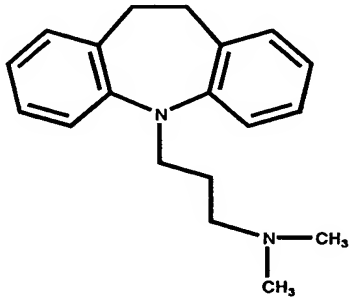
1. The Combination of the Foreman Patent in View of the 1997 Dostert Article Does Not Render the Claimed Invention Obvious

According to the action, the claimed invention is obvious over the Foreman patent in view of the 1997 Dostert article. The rejection is traversed, and reconsideration and withdrawal of the rejection are respectfully requested.

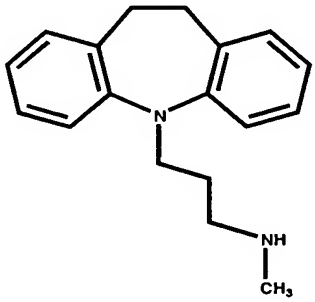
(a) The Official Action Does Not Set Forth a Prima Facie Case of Obviousness

According to the action, "[t]he prior art teaches that tricyclic anti-depressant compounds with norepinephrine reuptake inhibitory activity have been previously used for the treatment of lower urinary tract disorders." *See* the Action, at p. 4. Furthermore, the action states that "[t]he prior art also makes clear that reboxetine is a tricyclic anti-depressant having norepinephrine reuptake inhibitory activity." *Id.* The applicants strongly disagree that the prior art suggests that "reboxetine is a tricyclic anti-depressant." None of the applied prior art makes such a suggestion — to the contrary, and as described in more detail below, the applied prior art actually distinguishes reboxetine from tricyclic antidepressant compounds. For the reasons expressed below, however, no prima facie case of obviousness exists **even if** one were to conclude that reboxetine is a tricyclic antidepressant compound.

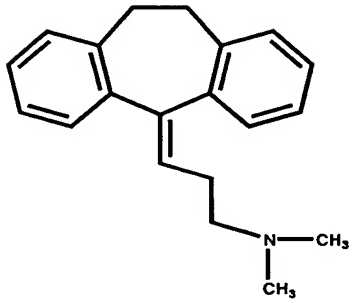
Of the two applied references (the Foreman patent and the 1997 Dostert article), **only** the Foreman patent discloses the use of tricyclic antidepressant compounds to treat lower urinary tract disorders. The Foreman patent identifies only four tricyclic antidepressant compounds: imipramine, desipramine, amitriptyline, and nortriptyline. *See generally*, col. 2, lines 59-64. The chemical structure of each of these compounds is shown in Figure 1, below:



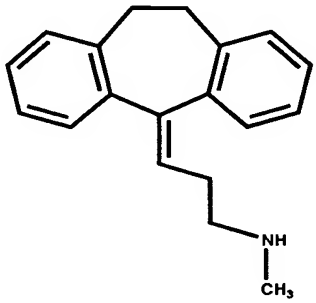
Formula A: Imipramine



Formula B: Desipramine



Formula C: Amitriptyline



Formula D: Nortriptyline

Figure 1

As shown in Figure 1, these compounds have chemical structures that are very similar to one another. Desipramine differs from imipramine only in the replacement of one of the methyl groups on the amino group with a hydrogen atom. Nortriptyline and amitriptyline differ from each other in the same way. Furthermore, imipramine differs from amitriptyline only in the replacement of the alkanyl linkage with a saturated C-N linkage. Desipramine and nortriptyline differ from each other in the same way. *See* Ross J. Baldessarani, "Drugs and the Treatment of Psychiatric Disorders," *in* Goodman & Gilman's The Pharmacological Basis of Therapeutics, 433-34 (table) (9th ed., McGraw-Hill, 1996) (publication is already of record).

The term "tricyclic antidepressant" is a term of art, which refers to a compound known to treat depression by blocking the reuptake of the norepinephrine and serotonin neurotransmitters in the central nervous system, and is characterized by a compound containing three fused rings of atoms. *See generally, id.* at 431-34 (identifying as "tricyclic antidepressants" those compounds having a three-ring molecular core and having an ability to

produce therapeutic responses in most patients suffering from major depression). A "fused ring" is a ring having one or more of its sides in common with another ring. *See generally*, Hawley's Condensed Chemical Dictionary, 525 (1997). As shown in Figure 1, above, each of the four compounds disclosed in the Foreman patent includes three fused rings of atoms that are characteristic of tricyclic antidepressant compounds. Thus, the Foreman patent's use of the term "tricyclic antidepressant" to refer to these four compounds is consistent with the term's use in the art.

The Foreman patent teaches that "tricyclic antidepressants in general, and imipramine in particular, are not approved for use in children under 5 years of age as these compounds are particularly toxic and potentially lethal in low dosage." *See* col. 3, lines 5-9. Moreover, in view of the art reviewed therein, the Foreman patent concludes that:

> ... it is apparent that while imipramine and other tricyclic antidepressants are used to treat a variety of lower urinary tract disorders, **the predominant mechanism responsible for these clinical effects remains unclear. Clearly these compounds have multiple mechanisms**. However, which mechanism primarily responsible for any of the mentioned utilities is subject to continuing experimentation and discussion.

See col. 6, line 14-20 (emphasis added). Still further, the Foreman patent states:

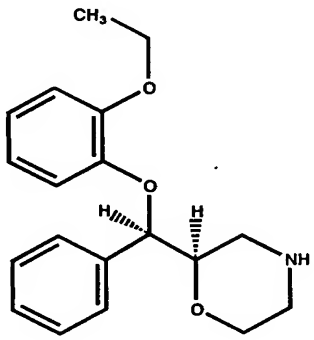
> **Thus, the literature is, at best, uncertain as to the biological mechanism underlying the ability for the tricyclic antidepressants to treat incontinence.** Moreover, it is clear that to the extent that any one or combination of these mechanisms may be useful for producing the end result, the compounds also have mechanisms which result in undesirable side effects. As noted above, imipramine and the other tricyclic antidepressants do possess a strong anticholinergic effect which likely results in the aforementioned side effects. Not only are such side effects annoying, but they may limit the effectiveness or even the use of such drugs. Accordingly, the need to discover drugs useful for treating incontinence without such side effects is evident.

See col. 6, lines 44-57 (emphasis added). The Foreman patent quite clearly expresses uncertainty as to which specific mechanism of tricyclic antidepressant compounds is responsible for the clinical effects.

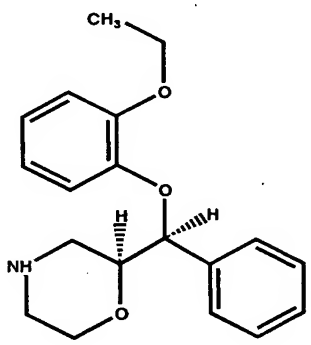
The U.S. Court of Appeals for the Federal Circuit has stated that a reference teaches away from the claimed invention when a person of ordinary skill in the art, upon examining the reference, "would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *See e.g., In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Thus, whatever the Foreman patent might disclose relative to prior uses of tricyclic antidepressant compounds to treat urinary

incontinence, it certainly does not suggest to a person having ordinary skill in the art which biological mechanism underlies its action and, indeed, maintains that serotonin reuptake inhibitory activity could be involved in regulating lower urinary tract functions. *See* col. 5, line 60 et seq. Furthermore, given the aforementioned uncertainties and undesirable consequences, a person having ordinary skill in the art would be motivated **against** using such compounds to treat lower urinary tract disorders if avoidance of adverse events is desired. Indeed, the Foreman patent itself ultimately discloses as its invention the use of a **bicyclic** compound (tomoxetine or pharmaceutically acceptable salt thereof) to treat urinary incontinence. Moreover, there is no disclosure or suggestion in the Foreman patent that selective inhibition of norepinephrine reuptake relative to serotonin reuptake could be important, or even desirable, in treating urinary tract disorders, while concomitantly minimizing adverse side effects. Therefore, a person having ordinary skill in the art would not be motivated to use (S,S) reboxetine to treat such disorders.

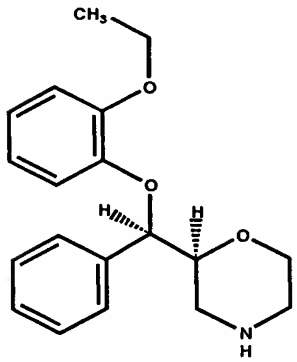
Further, reboxetine is not a "tricyclic antidepressant" compound. The chemical structure of each of the four reboxetine isomers is set forth in the specification at page 4, line 12, to page 6, line 13, and those structures are reproduced in Figure 2, below, for the sake of convenience.



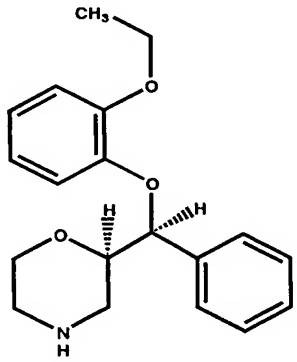
Formula E. (R,R) Reboxetine



Formula F. (S,S) Reboxetine



Formula G. (R,S) Reboxetine



Formula H. (S,R) Reboxetine

Figure 2

As noted above, the term "tricyclic antidepressant" is a term of art, which refers to a compound that is characterized by three fused rings of atoms. None of the four reboxetine isomers includes three fused rings of atoms that are characteristic of tricyclic antidepressant compounds. Consequently, none of the reboxetine isomers is a "tricyclic antidepressant" compound in accordance with the accepted definition of this term. Indeed, the applied prior art neither states nor suggests that reboxetine is a "tricyclic antidepressant" compound.

Reboxetine is not disclosed in the Foreman patent. Of the two references (the Foreman patent and the 1997 Dostert article) applied in support of the § 103(a) rejection of the claims, **only** the 1997 Dostert article discloses reboxetine. However, the 1997 Dostert article neither states nor suggests that reboxetine is a "tricyclic antidepressant" compound. Instead, the 1997 Dostert article **contrasts** reboxetine with "classical tricyclic antidepressants (TCAs)." *See, e.g.*, the 1997 Dostert article, at pp. S24 (right-hand column) and S28 (left-hand column, regarding affect on the cytochrome P-450 system in experimental animals). Accordingly, there is no support for the statement in the action that "[t]he prior art also makes clear that reboxetine is a tricyclic anti-depressant." If anything, the prior art (the 1997 Dostert article) makes clear that reboxetine is **not** a tricyclic antidepressant.

The § 103(a) rejection of the pending claims over the Foreman patent in view of the 1997 Dostert article should be withdrawn because the action **does not** set forth a prima facie case of obviousness. The action (incorrectly) asserts that reboxetine is a tricyclic antidepressant compound and, therefore, concludes that a person having ordinary skill in the art would be sufficiently motivated to substitute (S,S) reboxetine for one of the four tricyclic antidepressant compounds disclosed in the Foreman patent to treat incontinence **and** would have a reasonable expectation of success in safely treating incontinence. The Foreman patent discloses that tricyclic antidepressant compounds have been used in the past to treat lower urinary tract disorders. The Foreman patent, however, concludes that tricyclic antidepressant compounds are unsafe. Not only is reboxetine not a tricyclic antidepressant compound, but even if reboxetine could be considered to be a tricyclic antidepressant compound, a person having ordinary skill in the art would not be motivated to use tricyclic antidepressant compounds to treat incontinence due to the specific teachings in the Foreman patent that such compounds are unsafe. Furthermore, the action points to no evidence in the prior art that a person having ordinary skill faced with the same problem as the applicants herein — but not cognizant of the disclosure in this application — would have a reasonable expectation that he/she could successfully treat incontinence with a therapeutically effective amount of a composition comprising an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof. Still further, the Foreman patent provides no expectation that a compound that is highly selective for norepinephrine reuptake inhibition or against inhibitory activity at serotonin and other monoamine receptor sites can be used to treat incontinence.

The action makes no attempt to show where in the Foreman patent and the 1997 Dostert article any of the limitations recited in the dependent claims may be found. *See Ex parte Levy*, 17 USPQ2d at 1462 (stating that it is "incumbent upon the examiner to identify wherein each and every facet of the claimed invention is disclosed in the applied reference"). Because the action lacks such a showing, no prima facie case of obviousness has been made relative to any of the dependent claims.

In view of the foregoing, the applicants respectfully submit that independent claims 1 and 39, and all claims dependent therefrom are unobvious. Furthermore, the applicants respectfully request reconsideration and withdrawal of the § 103(a) rejection that is premised on a combination of the Foreman patent and the 1997 Dostert article.

(b) No Prima Facie Case of Obviousness Can Be Made Based on the Combined Disclosures of the Foreman Patent and the 1997 Dostert Article

According to the action, "[t]he prior art teaches that tricyclic anti-depressant compounds with norepinephrine reuptake inhibitory activity have been previously used for the treatment of lower urinary tract disorders." *See* the Action, at p. 4. Furthermore, the action states that "[t]he prior art also makes clear that reboxetine is a tricyclic anti-depressant having norepinephrine reuptake inhibitory activity." *Id.* Still further, the action asserts that "the substitution of one norepinephrine reuptake inhibitor for another would have been obvious to a person skilled in the art in the absence of evidence to the contrary." *Id.* No prima facie case of obviousness **can be made** based on the combined disclosures of the Foreman patent and the 1997 Dostert article, notwithstanding that the prior art might disclose that (a) compounds with norepinephrine reuptake inhibitory activity have been previously used for the treatment of lower urinary tract disorders, and (b) reboxetine has norepinephrine reuptake inhibitory activity. Contrary to the conclusions set forth in the action, the applied publications provide no evidence that would motivate a person having ordinary skill in the art to treat incontinence with a therapeutically effective amount of a composition comprising an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof.

The Foreman patent discloses numerous compounds possessing norepinephrine reuptake inhibitory activity and discloses that many of these compounds have been previously used for the treatment of lower urinary tract disorders. The Foreman patent concludes that many of these compounds (e.g., tricyclic antidepressant compounds) are unsafe, despite whatever norepinephrine reuptake inhibitory activity they may possess. *See generally*, Section III.B.1(a), above. Furthermore, the Foreman patent concludes that certain bicyclic compounds (e.g., tomoxetine) capable of inhibiting norepinephrine reuptake, while having a negligible anticholinergic effect, are better suited to treat urinary incontinence. *See* col. 7, lines 4-10. Indeed, the alleged contribution of the Foreman patent to the art is its finding that

certain (bicyclic) compounds with norepinephrine reuptake inhibitory activity and negligible anticholinergic reuptake inhibitory activity can be used to treat urinary tract disorders without the undesirable side effects arising from activity at the anticholinergic receptor sites. Despite this alleged contribution, however, there is no basis on which to conclude that a compound having a high selectivity for norepinephrine reuptake inhibition versus serotonin reuptake inhibition and inhibition at other monoamine sites could/would be useful to treat urinary tract disorders.

The 1997 Dostert article is directed to the pharmacokinetics and metabolism of reboxetine as it is used to treat depression in human beings. There is no mention of a possible use to treat incontinence. The 1997 Dostert article discloses that "reboxetine has been shown to be a selective noradrenaline reuptake inhibitor (NARI)," and that "[t]he (S,S) — enantiomer is more potent than its enantiomeric counterpart in inhibiting ... noradrenaline reuptake" in mice. *See* the 1997 Dostert article, at pp. S23 and S24. The 1997 Dostert article **does not** disclose the treatment of urinary incontinence and, further, **does not** disclose that norepinephrine reuptake inhibitors can be used to treat indications other than depression.

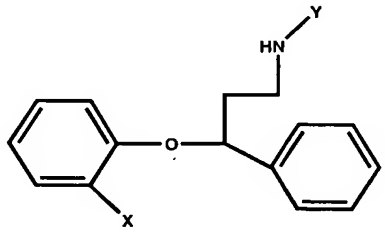
No prior art suggests to a person having ordinary skill in the art that he/she should selectively substitute (S,S) reboxetine in place of any of the structurally-dissimilar compounds (e.g., tricyclic antidepressant compounds, bicyclic compounds, etc.) disclosed in the Foreman patent to treat urinary incontinence and reasonably expect to safely treat urinary incontinence. Indeed, the official action itself acknowledges that a broadly-drawn function (e.g., norepinephrine reuptake inhibition) can include "small molecules, peptides, peptide mimetics or RNA-DNA based structures." *See* the Action, at p. 3. The action further states that such a broadly-drawn function, however, cannot possibly provide any direction for using any specific compound (e.g., "any peptides, peptide mimetics, or RNA-DNA based structures"). *Id.* The applicants submit that the reasoning applied in one portion of the action must apply consistently in other portions of the action. Thus, to the extent that the prior art generally discloses that the function of norepinephrine reuptake inhibition is responsible for treating urinary incontinence (which it does not), then the mere disclosure of such function does not provide any direction to a person having ordinary skill in the art to use any particular compound (e.g., (S,S) reboxetine), much less a compound structurally dissimilar from those expressly disclosed in the prior art. Absent a prior art suggestion, a person having ordinary skill in the art is no more motivated to substitute a tricyclic antidepressant compound or a bicyclic compound than he/she might be to substitute racemic reboxetine or any one of its four isomers in a method to treat urinary incontinence.

In view of the foregoing, the applicants respectfully request reconsideration and withdrawal of the § 103(a) rejection that is premised on a combination of the Foreman patent and the 1997 Dostert article.

2. The Combination of the Gehlert Patent in View of the 1997 Dostert Article Does Not Render the Claimed Invention Obvious

According to the action, the claimed invention is obvious over the Gehlert patent in view of the 1997 Dostert article. The entirety of the basis for the § 103(a) rejection of the claims is set forth in Section III, above. The rejection is traversed, and reconsideration and withdrawal of the rejection are respectfully requested.

The Gehlert patent's disclosure is merely cumulative to the disclosure found in the Foreman patent, which is discussed in Section III.B.1, above. Of the two applied references (the Gehlert patent and the 1997 Dostert article), **only** the Gehlert patent discloses the use of compounds to treat lower urinary tract disorders. Specifically, the Gehlert patent discloses that N-alkyl-3-phenyl-3-(2-substituted phenoxy)propylamines (shown in Figure 3, below) and pharmaceutically acceptable acid addition salts thereof are selective and potent norepinephrine reuptake inhibitors, and that these compounds are useful in treating urinary incontinence because of "the known interaction of the norepinephrine with the urinary system."



wherein X = I, Br, Cl, or C_1-C_4 alkylthio, Y = C_1-C_2 alkyl, and pharmaceutically acceptable acid addition salts thereof.

Formula I. N-alkyl-3-phenyl-3-(2-substituted phenoxy)propylamines

Figure 3

See col. 1, lines 35-52 and 63-37. None of the compounds within the genus of compounds shown in Figure 3, above, is structurally similar to reboxetine or any of its isomers (*see* Figure 2, above). Furthermore, none of the compounds within the genus of compounds in Figure 3, above, is structurally similar to the compounds disclosed in the 1997 Dostert article. The structural differences between the compounds disclosed in the Gehlert patent and those disclosed in the 1997 Dostert article certainly would not motivate a person having ordinary skill in the art to combine the teachings or to use the compounds interchangeably and expect success. Quite to the contrary, the dissimilarities would **dissuade** the person having ordinary skill in the art from using the compounds interchangeably.

The action asserts that "the substitution of one norepinephrine reuptake inhibitor for another would have been obvious to a person skilled in the art in the absence of evidence to the contrary." *Id.* The action cites to no evidence in support of this assertion and, instead, it improperly asserts that the burden of disproving obviousness rests with the applicants. The

burden of showing that the claimed invention is prima facie obvious rests squarely on the PTO. That showing "must be clear and particular, and broad conclusory statements about the teachings of multiple references, standing alone, are not 'evidence.'" Brown & Williamson Tobacco Corp., 229 F.3d at 1125 (quoting In re Dembiczak, 175 F.3d at 1000). Notwithstanding the impropriety of the assertion in the action, a legal conclusion of obviousness must include a determination of the scope and content of *all* of the prior art — there are other prior art publications (e.g., the Foreman patent) which, when also considered, cast serious doubt on the conclusion that "the substitution of one norepinephrine reuptake inhibitor for another would have been obvious to a person skilled in the art." *See Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1986). (stating that the references must be considered as a whole and must suggest the desirability and, thus, the obviousness of making the combination). As discussed above (in Section III.B.1(a) of this paper), the Foreman patent casts serious doubt on the mechanism by which urinary incontinence is regulated. Specifically, the Foreman patent states that "[t]he literature is, at best, uncertain as to the biological mechanism underlying the ability for the tricyclic antidepressants to treat incontinence." *See* col. 6, lines 44-46 of the Foreman patent.

The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and **all** teachings in the prior art must be considered to the extent that they are in analogous arts. The Foreman patent was filed within months of the Gehlert patent and shares the same assignee — Eli Lilly and Company, Indianapolis, Indiana. The Foreman patent is at least some evidence (if not strong evidence) that persons having ordinary skill in the art within the same organization did not even have a consistent understanding of the biological mechanism by which urinary incontinence could be treated. To wit, the Foreman patent asserts that even those practicing in the art outside of the organization (as represented by the literature reviewed in the patent) were uncertain as to the mechanism. In view of such uncertainty, a person having ordinary skill in the art would not have been motivated to substitute a material demonstrating a selectivity for norepinephrine reuptake over the α-adrenergic, β-adrenergic, and muscarinic cholinergic receptors (as disclosed in the 1997 Dostert article) in the place of a particular class of bicyclics having some undefined selectivity for norepinephrine reuptake (as disclosed in the Gehlert patent) to treat urinary incontinence. It is respectfully submitted that the totality of the prior art must be considered, and proceeding contrary to accepted wisdom/teachings in the art is strong evidence of non-obviousness. *See In re Hedges*, 783 F.2d 1038 (Fed. Cir. 1986); *see also, In re Rouffet*, 149 F.3d at 1357 (stating that "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for . combination **in the manner claimed**" (emphasis added)).

No prima facie case of obviousness can be made based on the combined disclosures of the Gehlert patent and the 1997 Dostert article, notwithstanding that the prior art might disclose that (a) compounds with norepinephrine reuptake inhibitory activity have been previously used for the treatment of urinary incontinence, and (b) reboxetine has norepinephrine reuptake inhibitory activity. Contrary to the conclusions set forth in the action, the applied publications provide no evidence that would motivate a person having ordinary skill in the art to treat incontinence with a compound that is highly selective for inhibiting reuptake at norepinephrine receptor sites relative to serotonin receptor sites or other monoamine receptor sites, such as a therapeutically effective amount of a composition comprising an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof. Furthermore, the action points to no evidence in the prior art that a person having ordinary skill faced with the same problem as the applicants herein — but not cognizant of the disclosure in this application — would have a reasonable expectation that he/she could successfully treat incontinence with a therapeutically effective amount of a composition containing an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof.

The action makes no attempt to show where in the Gehlert patent and the 1997 Dostert article any of the limitations recited in the dependent claims may be found. *See Ex parte Levy*, 17 USPQ2d at 1462 (stating that it is "incumbent upon the examiner to identify wherein each and every facet of the claimed invention is disclosed in the applied reference"). Because the action lacks such a showing, no prima facie case of obviousness has been made relative to any of the dependent claims.

In view of the foregoing, the applicants respectfully submit that independent claims 1 and 39, and all claims dependent therefrom are unobvious. Furthermore, the applicants respectfully request reconsideration and withdrawal of the § 103(a) rejection that is premised on a combination of the Gehlert patent and the 1997 Dostert article.

C. Evidence of Unexpected Results Rebuts the Alleged Prima Facie Case of Obviousness

Patent applicants can rebut a showing of prima facie obviousness in a number of ways including, but not limited to, a demonstration that the claimed invention provides substantially improved results and a statement that such results are unexpected:

> One way for a patent applicant to rebut a prima facie case of obviousness is to make a showing of "unexpected results," i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward — that which would have been surprising [or unexpected] to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields, such as chemistry, where

> minor changes in a product or process may yield substantially different results.
>
> ....
>
> [W]hen an applicant demonstrates **substantially** improved results ... and **states** that the results were unexpected, this should suffice to establish unexpected results **in the absence of** evidence to the contrary.

In re Soni, 54 F.3d 746, 750-51(Fed. Cir. 1995) (emphasis in original); *In re Davies*, 475 F.2d 667, 670 (CCPA 1973).

A declaration submitted pursuant to 37 CFR § 1.132 to present evidence of non-obviousness should compare the claimed subject matter with the applied prior art. In rebutting the prima facie case of obviousness, however, the applicants are not required to compare the claimed invention to what is allegedly suggested by the combination of references relied upon in rejecting the claims under § 103(a). *See In re Chapman*, 357 F.2d 418, 422 (CCPA 1966) (stating that requiring the applicants to compare the claimed invention with what is suggested by the combination of references relied upon in the rejection of the claims under § 103 "would be requiring comparison of the results of the invention with the results of the invention"). The demonstration of unexpected results preferably is made by submission of factual evidence commensurate in scope with the claims to which the results pertain and commensurate in scope with only so much of the scope of the claimed subject matter that is alleged to be prima facie obvious. *See generally, In re Dill*, 604 F.2d 1356, 1361 (CCPA 1979).

Attached as an appendix hereto is a copy of a "Declaration of Stephen P. Arneric Pursuant to 37 C.F.R. § 1.132" (the "Arneric Declaration"), which was filed in and during prosecution of the parent application (U.S. Serial No. 09/599,213, now U.S. Patent No. 6,465,458). Although the declaration was submitted in connection with the parent application, the text of the parent application is identical to that of the present application and the disclosed subject matter is identical. Specifically, paragraphs 1 and 4-6 of the declaration describe Dr. Arneric's background and demonstrate that he has reviewed the disclosed subject matter and is qualified to comment on the same. Paragraphs 8-15 of the Arneric Declaration and Tables I and II attached thereto relate to inhibition constants of compounds (including (S,S) reboxetine) for various monoamine transporter and receptor sites, and the selectivity of the compounds for the norepinephrine transporter site over the serotonin transporter site and other transporter or receptor sites. These portions of the Arneric declaration are discussed in detail, below, following a general description of the significance of inhibition constants and selectivity. The data and statements presented in the Arneric declaration are factual evidence of unexpected results and reasoned statements that such results are indeed unexpected. Accordingly, these data and accompanying statements

provide a showing of non-obviousness compelling withdrawal of the § 103(a) rejections of the claims.

1. Selectivity

The concentration of a compound required to inhibit 50% of the specific binding at a transporter or receptor site (i.e., IC_{50}) can be determined with radioligand binding assays by a non-linear, least square, regression analysis. This concentration (IC_{50}) is converted to an inhibition constant (K_i) utilizing the Cheng-Prusoff equation, which is shown as Equation 1, below:

$$K_i = \frac{IC_{50}}{\left(1 + \frac{[L]}{[K_d]}\right)}$$

Equation 1

wherein [L] is the concentration of free radioligand used in the assay, and [K_d] is the dissociation constant of the radioligand for the transporter or receptor site. *See* Y. Cheng and W.H. Prusoff (1973) *Biochem. Pharmacol.* **22**:3099-3108. The inhibition constant (K_i) is the concentration of the compound in the assay, which would occupy 50% of the transporter or receptor sites if no radioligand were present. Thus, the lower the inhibition constant (K_i) for a particular compound at a particular transporter or receptor site, the more potent the compound is at inhibiting reuptake at the site (e.g., the smaller the dose needed to induce an effect at the site). Conversely, the higher the inhibition constant (K_i) for a particular compound at a particular transporter or receptor site, the less potent that compound is at inhibiting reuptake at the site (e.g., the larger the dose needed to induce an effect at the site).

Inhibition constants can be used to make meaningful comparisons of compounds. For example, the selectivity of a particular compound favoring reuptake inhibition at one transporter or receptor site (*A*) relative to a second transporter or receptor site (*B*) can be determined by dividing the inhibition constants of the compound for the two sites, as shown in Equation 2, below:

$$S_{A/B} = \frac{(K_i)_A}{(K_i)_B}$$

Equation 2

wherein *S* refers to the selectivity of the compound favoring reuptake inhibition at site *A* relative to site *B*. *See generally*, Spec. at p. 30, line 28, to p. 32, line 24. In the foregoing equation, the selectivity (*S*) is a dimensionless number, where a value equal to one represents no selectivity (i.e., the compound exhibits equal affinity for both sites), values greater than one represent greater selectivity for site *B*, and values less than one represent greater selectivity for site *A*. (*See* Arneric Declaration, at ¶ 8.) Thus, a compound's high

selectivity favoring reuptake inhibition at a first transporter or receptor site (*A*) relative to a second transporter or receptor site (*B*) reveals that the compound is not likely to inhibit reuptake at the first site (*A*) and, therefore, is not likely to cause (side) effects associated with reuptake inhibition at the first site (*A*).

2. Unexpectedly High Selectivity Exhibited by (S,S) Reboxetine

Dr. Arneric's declaration includes two tables, which are discussed in paragraphs 8-15 therein. Table I of the declaration reports inhibition constants of different compounds for various monoamine transporter and receptor sites. The inhibition constants were obtained or determined in the manner set forth in paragraphs 12-15 of the declaration. Table II reports the inhibition constants of the same compounds relative to two sites — the norepinephrine and serotonin transporter sites — and also reports the selectivity of each compound for the norepinephrine transporter site and the serotonin transporter site. (*See* Arneric Declaration, at ¶ 8 and Table II.) Though not shown in either of the tables, the selectivity of each compound for the norepinephrine transporter site over the other monoamine transporter and receptor sites (i.e., 5-HT_{2A}, H_1, α_1-adrenergic, and muscarinic) can be easily calculated based on Equation 2, above. Furthermore, while the tables do not include inhibition constants for nortriptyline and imipramine, these compounds are structurally very similar to amitriptyline and desipramine, respectively, and, therefore, the data with respect to these compounds are not expected to meaningfully differ from the data reported relative to their structurally-similar counterparts. *See generally*, Figure 1, above, and the text accompanying the same. Thus, the compounds compared in the tables are commensurate in scope with the disclosure in the publications cited in support of the § 103(a) rejections.

The data reported in Tables I and II for (S,S) reboxetine stand in stark contrast to the corresponding data for desipramine and amitriptyline. (*See* Arneric Declaration, at ¶ 10 and Table II.) Specifically, (S,S) reboxetine exhibits surprisingly exceptional selectivity (>15,000) for the norepinephrine transporter site over that of the serotonin transporter site. (*Id.*) In contrast, amitriptyline and desipramine each exhibit a selectivity (1.8 and 430, respectively) that is magnitudes less than that exhibited by (S,S) reboxetine. (*See id.* at Table II.) Furthermore, the data reported in Table I conclusively show that (S,S) reboxetine is a highly selective inhibitor of the norepinephrine transporter site having almost 25,000 fold selective response over other transporter/receptor sites (5-HT_{2A}, H_1, α_1-adrenergic, and muscarinic) now believed to be responsible for adverse side effects. (*Id.* at ¶ 11) Such high selectivity is not exhibited by any of the comparative compounds. (*Id.* at ¶ 11) Specifically, amitriptyline and desipramine each exhibit a selectivity for the norepinephrine transporter site over that of the other four monoamine transporter or receptor sites that, again, is magnitudes less than that exhibited by (S,S) reboxetine. (*See id.* at Table I.) Consequently, and in contrast to amitriptyline and desipramine (and their structurally-similar counterparts, nortriptyline and

imipramine), one can definitively conclude that (S,S) reboxetine produces relief from urinary incontinence solely through its highly selective interaction with the norepinephrine transporter site. Moreover, the selectivity of (S,S) reboxetine should provide an overall improved safety and tolerability far beyond that of conventional tricyclic antidepressants. (*See* Arneric Declaration, at ¶ 11.)

3. The Evidence of Unexpected Results Compels a Conclusion that the Pending Claims are Not Obvious

The claimed invention is broadly recited in independent claims 1 and 39. As amended herein, claim 1 recites:

> 1. A method of treating an individual suffering from incontinence, the method comprising the step of administering to the individual a therapeutically effective amount of a composition comprising an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof.

Claim 39 recites:

> 39. A method of treating incontinence in an individual while diminishing adverse side effects, the method comprising the step of administering to the individual a total dose of about 0.1 to about 10 mg/day of an optically pure (S,S) reboxetine, or a pharmaceutically acceptable salt thereof.

All of the pending claims depend either directly or indirectly from one of claims 1 and 39.

In view of the foregoing, it is respectfully submitted that the data reported in Tables I and II of the Arneric declaration and the statements in paragraphs 10 and 11 of the declaration together provide a showing of non-obviousness that compels withdrawal of the § 103(a) rejections of the claims. Specifically, the data and statements in the Arneric declaration compare the claimed subject matter with the applied prior art. The reported data are commensurate in scope with the claims to which the unexpected results pertain and commensurate in scope with as much of the scope of the claimed subject matter that the action alleges is prima facie obvious. *See In re Dill*, 604 F.2d at 1361. The data show that (S,S) reboxetine exhibits superior selectivity for the norepinephrine transporter site relative to the serotonin receptor and the other monoamine transporter and receptor sites. The data also show that such selectivity is **magnitudes** greater than that exhibited by amitriptyline and desipramine. Indeed, the data show that such selectivity is also **magnitudes** greater than that exhibited by a racemic mixture of reboxetine. According to Dr. Arneric, such superior selectivity would not be expected of (S,S) reboxetine in view of the selectivity of the compared compounds (especially with respect to the racemic mixture of reboxetine). Due to the unexpectedly-superior selectivity of (S,S) reboxetine, Dr. Arneric further states that the selectivity of (S,S) reboxetine should provide an overall improved safety and tolerability far

beyond that of conventional tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, and nortriptyline). Indeed, such superior selectivity is an unexpected property neither disclosed nor taught in the prior art.

Accordingly, it is respectfully submitted, that the unexpected results/findings (e.g., (S,S) reboxetine having selectivity of serotonin (K_i)/norepinephrine (K_i) of at least about 5000 versus comparative compounds, such as amitriptyline and desipramine, for example, which have a selectivity of 1.8 and 430, respectively) provide strong evidence of non-obviousness compelling withdrawal of the § 103(a) rejections of the claims over the combined disclosure of the applied publications. Reconsideration and withdrawal of the § 103(a) rejections are therefore respectfully requested.

CONCLUSION

Prima facie obviousness under § 103 is a legal conclusion — not a fact. *In re Rinehart*, 531 F.2d at 1052. The foregoing response identifies facts (e.g., evidence in the form of statements in the prior art) rebutting the alleged legal conclusion that the claimed invention is prima facie obvious. Indeed, to the extent that a prima facie case of obviousness has been made or even exists, the foregoing response identifies facts (e.g., evidence in the form of data) and statements from someone qualified to comment on the subject matter of the claimed invention that together rebut a legal conclusion that the claimed invention is prima facie obvious. All of these facts must be evaluated along with the facts on which the legal conclusion was originally reached — not the legal conclusion itself. Having requested herein reconsideration of the legal conclusion set forth in the official action, the PTO is obligated to address all of the evidence and base its forthcoming legal conclusion(s) on such evidence, uninfluenced by its earlier conclusions. *Id.*

In view of the foregoing, the applicants respectfully request: consideration of the August 26, 2004, supplemental IDS and documents identified therein; entry of amendments to claims 1-8, 14-17, and 39; cancellation of claims 13, 32-37, 41, 44-51, and 57; entry of new claims 58-71; reconsideration and withdrawal of the rejections; and allowance of all pending claims (i.e., claims 1-12, 14-17, 39, 40, 54, 56, and 58-71).

Should the examiner wish to discuss the foregoing, or any matter of form or procedure in an effort to advance this application to allowance, she is urged to contact the undersigned attorney.

Respectfully submitted,

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March 21, 2005 By: _____

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APPENDIX

A copy of a paper entitled "Declaration of Stephen P. Arneric Pursuant to 37 C.F.R. § 1.132," which was filed in and during prosecution of the parent application (U.S. Serial No. 09/599,213, now U.S. Patent No. 6,465,458), follows.